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REMARKS

The Office Action Summary states that claims 8-13, 15-19, 23-33 and 40-106 are pending and that claims 8-13, 23-33, 40-72 and 74-79 are withdrawn from consideration. It also lists that claims 73 and 80-106 are rejected. Claims 15-19 are not listed as withdrawn or rejected; however, Applicant's understanding is that these claims have been withdrawn from consideration as well. Further, on page 2 of the Office Action in the "Detailed Action," the Examiner states that "claims 73 and 81-106 are under consideration in the instant office action." Applicant believes this was intended to state that claims 73 and 80-106 are under consideration.

Claim Rejections

Claims 73 and 80-106 have been rejected under 35 USC § 103(a) as being unpatentable over Gonda (US Pat No. 5,380,830, IDS Paper No 6), in view of Poeschia *et al.* (WO 99/15641, IDS Paper No. 8) and Temin *et al.* (US Pat No. 5,554,524).

The Examiner alleges that "Gonda teaches a full-length proviral BIV clone, the reference teaches the similarity between BIV and HIV." The Examiner acknowledges: "The reference does not teach constructing a transfer vector, or the production of a recombinant virion particle."

The Examiner alleges that "Poeschia *et al.* teaches the use of non-primate lentiviral vector (feline and ungulate) as a safer alternative than primate lentiviral vectors for the purpose of introducing a transgene into a cell. The reference teaches the use of non-primate lentivirus packagable nucleic acid, comprising a heterologous target nucleic acid operably linked to a promoter (see page 23 line 25 to page 24, line 28 and figure 1-2). The reference also suggests optionally including a portion of the *env* gene sequence into the packagable nucleic acid. The reference teaches the production of virion particle therefore *gag/pol* and *env* are present in the product. The reference teaches the use of the non-primate *gag/pol* sequences as well as the use of a VSV-G glycoprotein construct for the envelope." The Examiner acknowledges: "The reference does not specifically mention including the polypurine tract with the 3'UTR (see figure 1-2)." The Examiner alleges that "the reference also does not specifically exclude the polypurine tract from the packagable nucleic acid construct."

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The Examiner alleges that “Temin *et al.* teach chimeric retroviral vectors containing the long terminal repeats (LTRs) from complex retroviral (e.g. bovine leukemia virus (BLV); human immunodeficiency virus (HIV)) cis-acting regulatory sequences (e.g. att; primer binding site (PBS); encapsidation site (E), and polypurine tract (ppt) and coding regions. Cells transfected with these constructs are able to produce retrovirus particles (see figure 4-8, and column 5, lines 25-45).” The Examiner acknowledges: “The reference does not teach the use of BIV as a source for the packagable nucleic acid construct.”

The Examiner alleges: “It would have been obvious to one of ordinary skill in the art at the time of the invention was made to make a chimeric retroviral vector for expression of a transgene using the BIV sequence as taught by Gonda *et al.* is most similar to HIV.” The Examiner also states that “Poeschia *et al.* provide the motivation of using a non-primate lentiviral construct for the expression of transgene because they would provide safer source viral particles that can be used to introduce therapeutic nucleic acids constructs into human subjects because there is a reduced risk of recombination to produce an infectious virus. In addition, the Examiner alleges: “Temin *et al.* utilize a retroviral construct that has LTR sequences, a packaging sequence and a polypurine tract. Therefore the instant invention is *prima facie* obvious in view of the cited art.”

Applicant respectfully traverses.

A. Legal Requirements For Obviousness

Both the burden of proof and the evidentiary standard for determining obviousness are precisely defined. Specifically, the Examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) the teaching or suggestion of all the claim limitations of the Applicant's invention in the combined prior art references; and, 3) a reasonable expectation of success. MPEP § 2143.

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With regard to the first of these factors, suggestion or motivation to combine, such motivation may be found “where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, it must be *specific*. The Federal Circuit recently re-emphasized in *In re Lee* the importance of *specific* motivation to combine references, stating:

When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. *See, e.g., McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) (“the central question is whether there is reason to combine [the] references,” a question of fact drawing on the Graham factors).

“The factual inquiry whether to combine references must be thorough and searching.” *Id.* It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) (“a showing of a suggestion, teaching, or motivation to combine the prior art references is an ‘essential component of an obviousness holding’”) (quoting *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (“Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.”); *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (“teachings of references can be combined only if there is some suggestion or incentive to do so.”) (emphasis in original) (quoting *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).

In re Lee, 61 USPQ2d 1430, 1433-4 (Fed. Cir. 2002) (vacating and remanding the decision of the Board for failing to follow the relevant precedent).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however,

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sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. See *A-Site Corp. v. VSI International Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

MPEP § 2141 states that when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

- (A) The claimed invention must be considered as a whole;
- (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
- (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
- (D) Reasonable expectation of success is the standard with which obviousness is determined.

Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

B. The Cited References As A Whole Teach Away From Applicant's Invention

As noted above, MPEP § 2141 states that a basic consideration which applies to obviousness rejections is that "references must be considered *as a whole*." (Emphasis added.) However, as explained herein, Gonda and Poeschia *et al.* as a whole deter one skilled in the art from constructing and using BIV-based vectors.

The Examiner alleges: "Poeschia *et al.* provide the motivation of using a non-primate lentiviral construct for the expression of transgene because they would provide a safer source viral particles that can be used to introduce therapeutic nucleic acids constructs into human subjects because there is a reduced risk of recombination to produce an infectious virus." However, this statement appears to misapprehend the teachings of Poeschia *et al.* as a whole, for Poeschia *et al.* focuses particularly on FIV vectors, including advantages unique to them. Poeschia *et al.* states on page 20: "The practical applicability of this invention also benefits from

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the fact that lack of tropism of pathogenicity in humans is better established for FIV than any other non-primate lentivirus (these include Visna/Maedi, CAEV, EIAV and BIV) because may thousands of humans are exposed yearly by the same means by which FIV is predominantly transmitted among both feral and domestic cats in nature, *i.e.* cat bites." Also, on page 63, Poeschia *et al.* states: "FIV vectors therefore represent an inherently safer alternative to HIV vectors. Epidemiologic support for this hypothesis is strongest for FIV than for any other non-primate lentivirus, because FIV has shown no ability to infect or cause disease in humans after natural inoculation in many humans over many years by the same principal infective route operative in cats (cat bites)." In fact, the Examples in Poeschia *et al.* (pages 43-63) are wholly directed to FIV vectors. Thus, Poeschia *et al.* as a whole, particularly the statements noted above, specifically *teach away* from the use of BIV-based vectors and in fact provide a motivation *not* to construct and experiment with viral vectors based on BIV. Instead, Poeschia *et al.* only motivates one to use FIV as a source for the packagable nucleic acid construct.

Furthermore, the allegation on page 5 of the Office Action that the BIV sequence as taught by Gonda is "most similar to HIV" is incorrect. On the contrary, Gonda found that most BIV proteins have a low percentage of homology as compared to HIV proteins (see columns 15 and 16). For example, Gonda states in column 15: "when BIV 127 translation products for gag and pol ORF's were globally compared to those of other lentiviruses, only a small amount of homology was found when identical amino acid residues were calculated (range for gag = 23-29%; pol = 36-38%)." Also, when Gonda compared the BIV and HIV-1 gag proteins, only "one stretch of 10 amino acids within the P26 region of BIV was observed to have a high degree of homology to HIV-1." (See column 15 and Figure 10.) Additionally, Gonda teaches that BIV encodes two other ORFs designated W and Y, and neither have any nucleotide or amino acid similarities to primate or ruminant lentiviruses.

Still further, a review article by Gonda *et al.* (Virus Research, vol. 32, pages 155-181, 1994) (cited in the IDS of Nov. 19, 2001, and included herewith as **Exhibit A**), shows that BIV is the *most distantly related* lentivirus compared to HIV. In particular, Figure 2 on page 158 shows evolutionary analyses based on comparisons of conserved sequences in the reverse transcriptase (RT) domain of the *pol* genes of the lentiviruses and other retroviruses. Of the

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lentiviruses shown in the phylogenetic tree, BIV has the longest branch length (which is in units of $-\log M$, where M is the frequency of matching residues). Also, as stated at the top of page 159, "BIV is relatively equidistant from all of the other lentiviruses for this conserved segment of DNA."

Therefore, Applicant respectfully submits that Gonda (US Pat No. 5,380,830) and Gonda *et al.* (Virus Research, vol. 32, pages 155 – 181, 1994) actually emphasize the *differences* between HIV and BIV, and point to BIV as the lentivirus that is *least* related to HIV.

In summary, the two Gonda references along with Poeschia *et al.* teach away from the use of BIV as an alternative to HIV-based lentiviral vectors. To the extent that Poeschia *et al.* provides any motivation to use a non-primate lentivirus, such motivation is limited to the use of FIV, not all non-primate lentiviruses. Poeschia *et al.* specifically touts FIV as a superior non-primate lentiviral based vector and thereby leads one skilled of the art away from using BIV. Gonda *et al.* (1994) teaches that BIV is the least related lentivirus as compared to HIV. Therefore, one skilled in the art would not have been motivated to combine the non-primate lentivirus teachings of Poeschia *et al.* with the BIV-related teachings of Gonda with a reasonable expectation of success.

Temin *et al.* describes a vector that expresses some HIV proteins, but the vectors are based on non-lentiviral retroviruses and the inserted HIV nucleic acids cause the expression of a few HIV proteins. Furthermore, the Examiner acknowledges that the reference does not teach the use of BIV as a source for the packagable nucleic acid construct. Thus, Temin *et al.* does not supply the motivation missing from the other references to use BIV.

In view of the above, Applicant respectfully submits that the Examiner has not made out a *prima facie* case of obviousness. Therefore, Applicant respectfully submits that the outstanding rejection under 35 U.S.C. §103(a) cannot stand and should be withdrawn.

C. The Office Action Does Not Individually Address The Dependent Claims

The outstanding rejection under 35 USC § 103(a) appears directed to the subject matter recited in the independent claims, but the Office Action does not point out how the cited

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references apply to the subject matter recited in each of the dependent claims. MPEP § 707(d) states: "A plurality of claims should never be grouped together in a common rejection, unless that rejection is equally applicable to all claims in the group." However, all of claims 73 and 80-106 appear to have been grouped into a common obviousness rejection.

Applicant respectfully submits that the dependent claims recite subject matter that is in no way taught or suggested by the cited references. Nevertheless, Applicant also respectfully submits that regardless of their individual recitations, the dependent claims all recite novel and nonobvious subject matter simply because they depend from independent claims that, as set forth above, themselves claim subject matter not taught or suggested by the prior art as a whole. Therefore, Applicant respectfully requests that if the Examiner is not persuaded that the independent claims are patentable, and continues applying the cited references against the independent claims in another rejection, that the Examiner do so in the form of another non-final office action that addresses each of the dependent claims individually.

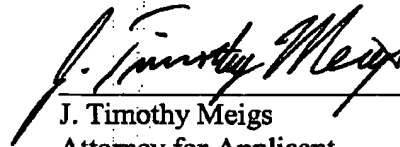
Conclusion

As noted earlier, the fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. Here, *prima facie* obviousness has not been established against any of the pending claims, as the Examiner has not provided a legally sufficient motivation to support a proper rejection. In fact, the cited references as a whole teach away from Applicant's invention.

Applicant therefore respectfully submits that the outstanding rejection under 35 U.S.C. §103(a) should be withdrawn and the case should be allowed. Notice to this effect is solicited at the Examiner's earliest opportunity. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

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